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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
CHAKRABARTI, A	
ART UNIT	**PAPER NUMBER**
1655	10

DATE MAILED: 08/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/463,549	Densham
Examiner	**Art Unit**
Arun Chakrabarti	1655

-- **The MAILING DATE of this communication appears on the cover sheet with the correspondence address** --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jul 19, 2001 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-21 and 30-34 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-21 and 30-34 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/463,549 .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant has elected Group I, corresponding to claims 1-21 and 30-34, without traverse. Non-elected claims 22-29 have been canceled without prejudice towards further prosecution.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-21 and 30-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 1, the preamble of the instantly claimed method is drawn to a method for sequencing a polynucleotide while the final process step is that of detecting an effect consequent on the incorporation of a specific nucleotide complementary to the target polynucleotide and it is thus unclear as to whether the instantly claimed methods are drawn to a method for sequencing a polynucleotide or rather detecting an effect consequent on the incorporation of a specific nucleotide complementary to the target polynucleotide. Method claim requires a last step or phrase in the last step that states the

accomplishments of the goals for the method which were stated in the method's preamble. Claim 1 lacks such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

Claim 1 is rejected over the lack of an antecedent basis "the" on lines 5 and 8.

Claim 3 is rejected over the lack of an antecedent basis "the" on line 2.

Regarding claims 6 and 8, the phrase "can be" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-9, 21 and 30-34 are rejected under 35 U.S.C. 102 (b) as being anticipated by Tsien et al. (PCT International Publication NO: WO 91/06678) (May 16, 1991).

Tsien et al teach a method for sequencing a polynucleotide (Abstract), comprising the steps of :

(I) reacting a target polynucleotide with a polymerase enzyme immobilized on a solid support, and the different nucleotides, under conditions sufficient for the polymerase reaction (Abstract, Figures 1A, 1B and 2 and Example 3 and Claims 1-2); and

(ii) detecting an effect consequent on the incorporation of a specific nucleotide complementary to the target polynucleotide (Abstract, Claims 1, 7 and 12 and Example 4).

Tsien et al teach a method wherein the effect in step (ii) is detected by measuring radiation (Example 4).

Tsien et al teach a method wherein steps (I) and (ii) are conducted with each of the different nucleotides in turn, until incorporation is detected, and then repeated (Claims 49-50).

Tsien et al teach a method wherein step (I) is conducted with all the nucleotides present (Claim 4 and Figures 2 and 3).

Tsien et al teach a method wherein the nucleotides comprise a 3' blocking group which is removed after the polymerase reaction (Example 4 and Claims 3-5 and Figures 1-3).

Tsien et al teach a method wherein the blocking group can be selectively removed by pulsed monochromatic light (Page 25, lines 4-12).

Tsien et al teach a method wherein the nucleotide comprise a further blocking group at the terminal phosphate group of the triphosphate chain, and the further blocking group is removed prior to the removal of the 3' blocking group (Example 2).

Tsien et al inherently teach a method wherein the further blocking group can be selectively removed by pulsed monochromatic light under conditions and durations different from those required to remove the 3' blocking group (Page 25, lines 4-12).

Tsien et al inherently teach a method wherein the polynucleotide is DNA (Abstract and Figure 1).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7 . Claims 1-9, 15, 17- 18, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al. (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Schwarz et al. (Trends in Biotechnology, (October ,1991), Vol. 9, pages 339-340).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum.

Schwarz et al. teach the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum (Figure 2 and Page 340, Columns 1-3).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al , since Schwarz et al. state, "The particular advantages of SPR-based biosensors are (1) rapid reading and (2) real-time kinetic analysis. Detection sensitivity approaches that of conventional methods, and simple protocols can be used because probe labeling is unnecessary. The operation of such biosensor is suitable for automation and can be developed to detect hybridizations of a sample to a number of DNA probes simultaneously (Page 340, Column 2, last three sentences)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al in order to improve the analysis of a plurality of target nucleic acid. An ordinary practitioner would have been motivated to combine and substitute the detection of nucleic acid incorporation by surface plasmon resonance signal over time in the infra-red spectrum of Schwarz et al. into the DNA sequencing method of Tsien et al , in order to achieve the express advantages noted by Schwarz et al., of a method that provides advantages of SPR-based biosensors (1) rapid reading and (2) real-time kinetic analysis where probe labeling is unnecessary and the operation of such biosensor is suitable for automation and can be developed to detect hybridizations of a sample to a number of DNA probes simultaneously.

8. Claims 1-10, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Chang et al. (U.S. Patent 5,801,042) (September 1, 1998).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach the competitive inhibitor of the polymerase enzyme.

Chang et al. teach the competitive inhibitor of the polymerase enzyme (Column 24, lines 25-60).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al, since Chang et al. state, "These nucleoside analogs act as competitive inhibitors of DNA polymerase substrates. The analogous may act as a chain terminator, cause increased lability (e.g., susceptibility to breakage) of analogue-containing DNA, and/or impair the ability of the substituted DNA to act as template for transcription or replication (Column 24, lines 47-60)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al in order to inhibit the DNA polymerase to fcontrol and regulate the detection of the incorporated nucleotide. An ordinary practitioner would have been motivated to combine and substitute the competitive inhibitor of the polymerase enzyme of Chang et al. into the DNA sequencing method of Tsien et al. , in order to achieve the express advantages noted by Chang et al., of a competitive inhibitor

of DNA polymerase substrates that may act as a chain terminator, cause increased lability (e.g., susceptibility to breakage) of analogue-containing DNA, and/or impair the ability of the substituted DNA to act as template for transcription or replication.

9. Claims 1-9, 11-12, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of O'Donnell (U.S. Patent 6,221,642 B1) (April 24, 2001).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide.

O'Donnell. teach the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide (Abstract , Figure 1 and Column 4, lines 26-61).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al, since O'Donnell states, "The beta clamp confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses (Column 4, lines 40-43)." O'Donnell further states, "This high degree of symmetry in the beta ring could help promote smooth gliding along the symmetrical DNA duplex (Column 4, lines 61-63)". By employing scientific reasoning, an ordinary artisan would have combined and substituted the beta-2 dimer complex of the E.coli DNA polymerase

III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al, to improve the structure and function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the beta-2 dimer complex of the E.coli DNA polymerase III with the target polynucleotide of O'Donnell into the DNA sequencing method of Tsien et al., in order to achieve the express advantages noted by O'Donnell, of the beta clamp that confers processivity onto the core polymerase by binding directly to the polymerase alpha subunit, thereby tethering the polymerase to DNA for processive syntheses and also to achieve the advantage of the high degree of symmetry in the beta ring that could help promote smooth gliding along the symmetrical DNA duplex.

10. Claims 1-9, 13, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Rosenthal et al. (PCT International Publication Number: WO 93/21340) (October 21, 1993).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach the Taq polymerase.

Rosenthal et al. teach the Taq polymerase (Page 9, lines 5-10).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al, since Rosenthal et al state, "Suitable DNA polymerases are, for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase)

(Page 9, lines 7-10)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al, to improve the function of the DNA polymerase. An ordinary practitioner would have been motivated to combine and substitute the Taq polymerase of Rosenthal et al. into the DNA sequencing method of Tsien et al, in order to achieve the express advantages noted by Rosenthal et al., of suitable DNA polymerases for example, Sequenase 2.0, T4 DNA polymerase or the Klenow fragment of DNA polymerase 1 as well as heat-stable polymerase such as Taq polymerase (for example Taquenase).

11. Claims 1-9, 14, 21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Vind (U.S. Patent 6,159,687) (December 12, 2000).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach the reverse transcriptase as the polymerase.

Vind teaches the reverse transcriptase as the polymerase (Column 7, lines 15-21).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al, since Vind states, "The choice of polymerase is therefore an important means in controlling the average extension of the primers. These conditions may also exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low

fidelity), a parameter useful in combining shuffling and mutagenesis (Column 7, lines 15-21)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al, to improve the function of the DNA polymerase and the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the reverse transcriptase as the polymerase of Vind into the DNA sequencing method of Tsien et al, in order to achieve the express advantages noted by Vind, of the choice of polymerase which is an important means in controlling the average extension of the primers which also may exert an influence on the fidelity of the polymerase (the rate by which point mutations are introduced; HIV reverse transcriptase is an example of a polymerase of low fidelity), a parameter useful in combining shuffling and mutagenesis.

12. Claims 1-9, 16, 19-21 and 30-34 are rejected under 35 U.S.C. 103 (a) over Tsien et al . (PCT International Publication NO: WO 91/06678) (May 16, 1991) in view of Smith et al. (U.S. Patent 5,753,439) (May 19, 1998).

Tsien et al teach the method of claims 1-9, 21 and 30-34 as described above.

Tsien et al do not teach the detection of nucleotides by NMR using electromagnetic radiation.

Smith et al. teach the detection of nucleotides by NMR using electromagnetic radiation (Column 7, lines 14-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al, since Smith et al. state, "These methods can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen for genetic defects and disorders. Assays can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated (Abstract, last two sentences)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al to improve the sequencing of DNA. An ordinary practitioner would have been motivated to combine and substitute the detection of nucleotides by NMR using electromagnetic radiation of Smith et al. into the DNA sequencing method of Tsien et al in order to achieve the express advantages noted by Smith et al., of the methods which can be used to detect characteristic nucleic acid sequences, to determine target sequence and to screen for genetic defects and disorders and which can be conducted on solid surfaces allowing for multiple reactions to be conducted in parallel and, if desired, automated.

Conclusion

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703)

306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMA
PRIMARY EXAMIN

Arun Chakrabarti,

Patent Examiner,

August 17, 2001